Side effects of Androgen Deprivation Therapy (ADT)

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Case JB

- 86 yr old Male
- Metastatic Prostate Cancer with PSMA PET avid retroperitoneal lymphadenopathy
- Presented with back pain and LUTS
- Other medical conditions: diabetes mellitus type 2, heart failure, dyslipidaemia, polymyalgia rheumatica, pacemaker in place, atrial fibrillation non-valvular, GORD, Depression.
- Medications: Venlafaxine 37.5mg daily, Panadol Osteo prn, Tagin 10/5mg/BD, Rivaroxaban 20mg/daily, Sacubitril/Valsartan 24.3mg/25.7mg/BD, Gliclazide MR 30mg QDS, Bisoprolol 2.5mg/BD, Rosuvastatin 5mg/daily, Linagliptin 5mg/daily, Furosemide 40mg/daily, Metformin 1g/daily, Dapagliflozin 10mg/daily and Lantus insulin 15 units nocte.

- Lives with wife
- Walks with 4WW
- G8 8/17
- CGA showed Rockwood FI 0.6 s/o moderate Frailty
- ECOG 2

Treatment options

- Androgen Deprivation Therapy (ADT)
- Chemotherapy
- Androgen Receptor Pathway Inhibitors (ARPI)

- HOW SHOULD WE TREAT THIS PATIENT?

ANDROGEN DEPRIVATION THERAPY (ADT)

- Indications:
  - Low volume disease or Rising PSA only progression
  - With adjuvant or neoadjuvant chemotherapy and/or ARPI
  - Not fit for more aggressive therapy
- Different types:
  - medications (tablets or injections) that reduce the production of testosterone.
  - Surgical removal of the testes (orchidectomy) to stop the production of androgens.
- Injections include:
  - Goserelin (Zoladex®)
  - Leuporelin (Eligard®, Lucrin®)
  - Triptorelin (Diphereline®)
  - Degarelix (Firmagon®)
- Tablets include:
  - Bicalutamide (Cosudex)
  - Cyproterone acetate (Androcur)

eviQ: https://www.eviq.org.au/getmedia/8cd3b382-e0a2-4668-abb9-0b974a9e28fb/3384-ADT-prostate-Nov-2022.pdf.aspx?ext=.pdf.

- Patient was started on Bicalutamide, Gorserelin was commenced after few weeks

- WHAT SHOULD WE CAREFUL ABOUT?
- Flare reaction
- Side effects

- Osteoporosis
- Changes in body appearance, physical strength, mood and cognition
- Increased risk of heart and endocrinologic disease
- Sexual dysfunction: reduction or loss of libido, impotence, infertility
- Hot Flushes and Fatigue

Osteoporosis and Bone Fractures

- ADT increases bone turnover, decreases bone mineral density, and increases the risk of bone fractures
- Loss of bone mineral density usually after six to nine months of ADT, and longer therapy confers a higher risk.
- Osteoporotic skeletal fractures occur in up to 20 percent of males within five years of starting ADT.
- Other contributing factors: reduced intake of calcium, low vitamin D levels, alcohol abuse, smoking, and chronic use of corticosteroids.
- BMD scan once every two years
- Calcium/Vit D supplements, Bisphosphonates

EMOTIONAL AND COGNITIVE CHANGES

- Some evidence of ADT accelerating development of dementia
- Increased incidence of depression and anxiety
- A meta-analysis of 14 studies of males with prostate cancer who did or did not receive ADT. The risk of new-onset dementia or Alzheimer disease modestly but significantly higher in males receiving ADT compared with those who did not (HR 1.21, 95% CI 1.11-1.33, and HR 1.16, 95% CI 1.09-1.24).
- Longer exposure (>12 months) increase the risk further

BODY COMPOSITION AND METABOLISM

- Gynaecomastia and thinning of body hair (increased ratio of estrogen to androgen activity)
- Loss of lean body mass (Sarcopenia)
- Increased body fat in subcutaneous adipose tissues
- Decreased muscle strength
- Decreased insulin sensitivity
- Increase in serum LDL-cholesterol and triglycerides
- Hyperglycemia and increased risk of developing diabetes

Cardiovascular Risk

- Meta-analysis on observational data from eight large studies (n=415,000) patients managed with any form of ADT(GnRH agonist, orchiectomy, oral antiandrogens), the relative risk for any type of CVD was 1.38 (95% CI 1.29-1.48).
- Increased risk in patients with pre-existing CVD and other contributing factors
- **STAMP screening question: S**troke; **T**ransient ischemic attack; **A**bdominal aortic aneurysm or other aortic disease; **M**yocardial infarction or angina; **P**eripheral vascular disease
- Careful decision making, Geriatrician consultation and Close monitoring
- HERO study: Less cardiac risk with Degarelix compared to other ADTs

Thromboembolic events

- Increased risk of deep venous thrombosis, pulmonary embolus, arterial embolism.
- SEER database study of 155,000 men, significantly increased risk of thromboembolic events in Men on ADT compared with those not on ADT(15 versus 7 percent, HR 1.56)
- Watchful monitoring and proactive investigation is paramount
- Patients on Anti-coagulants should conitnue

Sexual Dysfunction

- Loss of Libido and erectile dysfunction occur within few months of starting ADT
- Reduction in size of penis and testicles follow
- Recovery of sexual function usually happen after discontinuation of ADT
- Couple counseling and well informed decision making is necessary

Other side effects

- Hot flashes
- Insomnia
- Nausea
- Excessive sweating
- Fatigue
- Anemia, usually mild to moderate, normochromic, and normocytic

Risk Reduction Strategies

- High risk Males starting on ADT, should be followed and managed by a multidisciplinary team and treated according to best practices including:
- If lipids are abnormal, use statin therapy to lower low-density lipoprotein cholesterol.
- If blood pressure exceeds goal based on cardiovascular risk, add anti hypertensive therapy
- If fasting glucose is elevated and hemoglobin A1c is abnormal, approaches to lowering glucose are appropriate.
- Patients with known CVD should take aspirin (generally 81 mg/day) unless contraindicated.
- Males who continue to smoke should be referred to smoking cessation programs.
- Structured exercise program: Moderate exercise, to include three or more hours of aerobic activity weekly, plus resistance training and weight-bearing exercises

Case JB

- As per CGAM, patient referred to Physiotherapist, Psychologist and Geriatrician
- Continued on Goserelin injection once three monthly
- Ongoing symptom improvement and reduction in PSA
- QoL maintained with multidisciplinary approach